REMARKS

Reconsideration is requested.

Claims 23-34, 36-38 and 40-44 are pending. Claims 23-33 and 42-44 have been withdrawn from consideration.

The Amendment After Final Rejection of February 4, 2010 has not been entered. See Advisory Action dated February 19, 2010.

The subject matter of the Examiner's Group I of the Office Action dated August 6, 2008 has been elected and examined in so far as the claims of the elected subject matter read on SEQ ID NO:9, which is a cyclic peptide containing the sequence CSFEEC wherein the terminal "C" amino acids are cyclized.

Rejoinder and allowance of any claim defining a method of making and/or using a product defined by an allowable claim, at an appropriate time, are requested.

Claims 34 and 38 have been revised, without prejudice, to obviate the Section 112, second paragraph, rejection of claims 34, 38 and 41. Entry of the present Amendment and withdrawal of the rejection are requested.

The Section 102 rejection of claims 34, 38 and 41 over Krstenansky (BBA 957 (1988) 53-59), is obviated by the above amendments. Entry of the present Amendment and withdrawal of the rejection are requested. As the applicants understand the unamended claims to have been examined only in so far as they read on the elected species (i.e., SEQ ID NO:9 - see page 2 of the Office Action dated December 8, 2009), Krstenansky is not believed to establish a *prima facie* case of anticipation as the Examiner has only pointed to a cyclized peptide "CDFEEIPEEYLC" of the cited

reference as allegedly anticipating the examined subject matter. See page 4 of the Office Action dated December 8, 2009. Clarification is requested in the event the rejection is maintained even in the present Amendment is not entered. Entry of the present Amendment and withdrawal of the Section 102 rejection is requested.

The Section 103 rejection of claims 34, 36-38, 40 and 41 over Gupta (Bioorganic and Medicinal Chemistry Vol. 8 (2000) pages 723-729), Bronson (Molecular Human Production, Vol. 5, (1999) pages 433-440) and Myles (PNAS, Vol. 91, pages 4195-4198 (1994)), is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

According to Gupta, it had been previously appreciated that

> "small peptides corresponding to the disintegren binding loop of the fertilinβ inhibit fertilization in vitro in guinea pigs, mice, monkeys and human." See page 724, left column of Gupta.

Gupta describes the prior art as supporting

> "the conclusion that the disintegrin domain of the extracellular sperm protein fertilinβ binds to $\alpha_6\beta_1$ integrin on the plasma membrane of the egg." Id.

Gupta teaches that the minimal peptide motif for binding $\alpha_6\beta_1$ "(analogous to RGD)" has not been ascertained however a sequence alignment between disintegrin domains reproduced in Figure 1 of Gupta reveals that TDE sequence of guinea pig fertilinβ diintegrin directly aligns with the RGD motif. See page 724, paragraph spanning the left and right columns of Gupta.

This TDE sequence is the focus of the Myles reference cited by the Examiner, as will be discussed further below.

Gupta describes that TDE containing sequence of other researchers have been found to inhibit "sperm-egg fusion". See page 724, right column of Gupta and highlighted portion of below alignment from Figure 1 of Gupta.

Figure 1 of Gupta describes, in part, the following alignments of ADAM disintegrins and SVMP P-II disintegrins containing an RGD motif (as sequences between conserved cysteines):

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Guinea pig:     RESTDECDLPEY
Human:          RPSFEECDLPEY
Kristin:        RIPRGD-MPDDR
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Gupta teaches that while previous studies had focused on the TDE, determination and alignment of fertilinβ sequences from more species

> "revealed that the ECD sequence [underlined in above alignment from Figure 1] is highly conserved in the binding loop of fertilinβ. The alignment suggested that ECD could be the minimal recognition sequence for the $\alpha_6\beta_1$ integrin on the egg." Id.

Bronson, which is cited by the Examiner and was published before Gupta, focuses on the FEE sequence but concludes that

> "The present experiments, however do not allow us to distinguish the relative importance of the FEE and ECD tripeptides in receptor recognition for human gametes, as the octapeptide used (SFEECDLP) in studying the interaction of homologous human gametes contains both amino acid sequences derived from the disintegrin domain of human fertilin-β." See page 438 of Bronson.

One of ordinary skill in the art reviewing these conclusions of Bronson and Gupta would focus on the ECD tripeptide of Gupta as opposed to the FEE sequence mentioned by Bronson.

Gupta continues further teaches that

> "as more fertilinβ sequences became available, the alignments hinted that perhaps **(D/E)ECD** was actually the consensus sequence." See page 724, right column of Gupta (emphasis added).

Gupta concludes that the free thiol provided by the cysteine in the DECD sequence is required for inhibition. See page 727, left column, third paragraph ("This result clearly shows that the conserved cysteine is required as a free thiol for inhibition of in vitro fertilization.") of Gupta. This conclusion of Gupta would have discouraged one of ordinary skill in the art to have produced a cyclized sequence involving the cysteine (**C**) of the **DECD** sequence of Gupta, or the **SFEECDLP** sequence variation of Bronson or the **CSTDEC** sequence variation of Myles. In fact, Myles teaches in Table 2 of the reference that a linear sequence **STDECDLK** has greater activity in both the percent inhibition of fusion as measured by eggs fused and as measured by percentage inhibition of sperm fused per egg.

As noted above, the claims have been examined in so far as the claims read on the elected sequence **CSFEEC** (SEQ ID NO:9) wherein the terminal cysteine (**C**) residues are cyclized. The conclusion of Gupta that a free thiol is required for inhibition and the conclusion of Myles that a linear peptide provides improved results over a similar cyclized peptide, would have led one of ordinary skill away from the claimed invention and specifically away from the elected species. The combination of Gupta, Bronson and Myles would not have made the claimed invention obvious.

The further conclusion of Gupta that a cyclized version of the **DECD** peptide (i.e., **CDECDC**) provided no significant difference in percent inhibition is attributed by Gupta to a conformational constraint resulting from limited sequence length. This conclusion

by Gupta would have further led one of ordinary skill in the art to have made longer sequences, which would have been preferably linear in view of the further teachings of Myles.

The applicants further note that the peptides of the cited art are inhibitors of fertilization (i.e., inhibitors of fusion of gametes). Gupta discloses cyclic peptides exhibiting an inhibitory effect on fertilization. See page 725, left column, second paragraph of Gupta. Bronson relates to a linear peptide containing a tripeptide FEE and inhibiting sperm adhesion and penetration to oocytes. Linear peptides disclosed in Bronson are therefore inhibitors of fertilization. Myles relates to the use of peptide analogues to study the role of fertilinβ. Myles teaches the cyclized peptide CSTDEC as a strong sperm-egg inhibitor. Contrary to the cited art, the cyclic peptide of the present invention increases the fusiogenic capacity of the gamete and could therefore be used as an activator of fertilization. The cyclic peptides of the present invention therefore exhibit unexpected properties.

The claimed products would not have been obvious in view of the combination of cited art and withdrawal of the Section 103 rejection is requested.

For completeness, the applicants note that product of claim 41 would not have been obvious in view of the cited art. Rather, the composition of claim 41 would have been contrary to the cited combination of art which teaches the use of peptides for inhibiting the binding of sperm and egg. One of ordinary skill in the art would not have made a gamete culture media comprising a peptide of the cited art as such a culture would have been aimed at inhibiting gamete fusion. Contrary to the teachings and aim

of the cited art, the applicants have provided products which increase the fusogenic capacity of gametes.

Evidence of the unexpected properties of the claimed products may be found, for example, in the present application. Specifically, the examples of the present specification demonstrate the statistically significant increase in fusion of spermatozoa fusion with oocytes after pre-incubation of the oocytes with the elected SEQ ID NO:9. See pages 11-14 of the present specification.

The claimed invention would not have been obvious from the cited art. The combination of cited art teaches away from the claimed products. Entry of the present Amendment and allowance of all of the claims are requested.

The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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